

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
31 July 2003 (31.07.2003)

PCT

(10) International Publication Number
WO 03/062411 A1

(51) International Patent Classification⁷: **C12N 9/12**,
15/62, C07K 16/18, G01N 33/50, C12N 5/10, A61K
38/45, C12N 15/11, C12Q 1/68, G01N 33/00

(21) International Application Number: PCT/GB03/00211

(22) International Filing Date: 21 January 2003 (21.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0201384.5 22 January 2002 (22.01.2002) GB

(71) Applicant (for all designated States except US): **EURO-
PEAN MOLECULAR BIOLOGY LABORATORY**
[DE/DE]; Postfach 102209, 69012 Heidelberg (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DOREY, Karel**
[FR/GB]; 2 Somerfield Road, London N4 2JJ (GB).
PLUK, Wilhelmina [NL/NL]; Walstro 59, NL-5432
DR Cuyk (NL). **SUPERTI-FURGA, Giulio** [IT/DE];
Muhldamm 7, 69118 Heidelberg (DE).

(74) Agents: **GOODFELLOW, Hugh, Robin et al.**; Carp-
maels & Ransford, 43 Bloomsbury Square, London WC1A
2RA (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI,
SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: **TYROSINE KINASE INHIBITORS**

(57) Abstract: The present invention relates to novel proteins that inhibit the activity of tyrosine kinases. In particular, the invention provides a tyrosine kinase inhibitor protein consisting of the cap region of a c-Abl protein. The invention also relates to the use of tyrosine kinase inhibitor proteins in the treatment and diagnosis of diseases, in particular cancers, in humans.

WO 03/062411 A1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/00211

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N9/12 C12N15/62 C07K16/18 G01N33/50 C12N5/10
 A61K38/45 C12N15/11 C12Q1/68 G01N33/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>PLUK HELMA ET AL: "Autoinhibition of c-Abl." CELL, vol. 108, no. 2, 24 January 2002 (2002-01-24), pages 247-259, XP001147512 January 24, 2002 ISSN: 0092-8674 The whole document. The document was made available to the public online at 12 noon EST on January 24 2002.</p> <p style="text-align: center;">--- -/--</p>	1-27, 31-54



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"8" document member of the same patent family

Date of the actual completion of the international search

5 June 2003

Date of mailing of the international search report

24/06/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Valcarcel, R

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/00211

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VAN ETEN RICHARD A: "Cycling, stressed-out and nervous: Cellular functions of c-Abl." TRENDS IN CELL BIOLOGY, vol. 9, no. 5, May 1999 (1999-05), pages 179-186, XP002243530 ISSN: 0962-8924	1-26, 31-41
A	the whole document	1-27, 31-54
X	WO 01 94408 A (EUROP MOLECULAR BIOLOGY LAB ;SUPERTI FURGA GIULIO (DE); BARILA DAN) 13 December 2001 (2001-12-13)	1-26, 31-41
A	the whole document	27,42-54
X	WEN S-T ET AL: "The PAG gene product, a stress-induced protein with antioxidant properties, is an Abl SH3-binding protein and a physiological inhibitor of c-Abl tyrosine kinase activity" GENES AND DEVELOPMENT, COLD SPRING HARBOR, NY, US, vol. 11, no. 19, 1 October 1997 (1997-10-01), pages 2456-2467, XP002182087 ISSN: 0890-9369	1-26, 31-41
A	the whole document	27,42-54
X	TOPALY J ET AL: "SYNERGISTIC ACTIVITY OF THE NEW ABL-SPECIFIC TYROSINE KINASE INHIBITOR ST1571 AND CHEMOTHERAPEUTIC DRUGS ON BCR-ABL-POSITIVE CHRONIC MYELOGENOUS LEUKEMIA CELLS" LEUKEMIA, MACMILLAN PRESS LTD, US, vol. 15, May 2001 (2001-05), pages 342-347, XP001039741 ISSN: 0887-6924	1-26, 31-41
A	the whole document	27,42-54
X	BARILA D ET AL: "AN INTRAMOLECULAR SH3-DOMAIN INTERACTION REGULATES C-ABL ACTIVITY" NATURE GENETICS, NEW YORK, NY, US, vol. 18, March 1998 (1998-03), pages 280-282, XP001021006 ISSN: 1061-4036	1-26, 31-41
A	the whole document	27,42-54

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/00211

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WALKENHORST JUERGEN ET AL: "Analysis of human c-Abl tyrosine kinase activity and regulation in <i>S. pombe</i> ." ONCOGENE, vol. 12, no. 7, 1996, pages 1513-1520, XP009011935 ISSN: 0950-9232	1-26, 31-41
A	the whole document	27, 42-54
A	DOREY KAREL ET AL: "Phosphorylation and structure-based functional studies reveal a positive and a negative role for the activation loop of the c-Abl tyrosine kinase." ONCOGENE, vol. 20, no. 56, 2001, pages 8075-8084, XP009011896 6 December, 2001 ISSN: 0950-9232	1-27, 31-54
A	the whole document	
A	WU J J ET AL: "Comparison of the intrinsic kinase activity and substrate specificity of c-Abl and Bcr-Abl" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 17, 8 September 1998 (1998-09-08), pages 2279-2284, XP004138218 ISSN: 0960-894X	1-27, 31-54
A	the whole document	
A	DOREY K ET AL: "REGULATION OF HUMAN C-ABL TYROSINE KINASE ACTIVITY IN XENOPUS OOCYTES AND ACCELERATION OF PROGESTERONE-INDUCED G2/M TRANSITION BY ONCOGENIC FORMS" BIOLOGICAL CHEMISTRY, XX, XX, vol. 380, no. 2, February 1999 (1999-02), pages 223-230, XP001022104 ISSN: 1431-6730	1-27, 31-54
E	the whole document	
	WO 03 031608 A (BRANFORD SUSAN ;HUGHES TIMOTHY (AU); RUDZKI ZBIGNIEW (AU); MEDVET) 17 April 2003 (2003-04-17) the whole document	1-26, 31-41

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/00211

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 28-31, 33-38
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 03 00211

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 36-38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claim 40 is directed to a diagnostic method comprising a method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 28-31, 33-38

Claims 28 and 30 relate to a product defined by being identified or identifiable by the methods of claims 27 and 29 respectively. Claim 29 refers to a method defined in terms of the activator of claim 28.

The claims cover all products having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT nor disclosure within the meaning of Article 5 PCT for any of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a product of manufacture. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Thus, the subject-matter of claims 28, 29, and 30 has not been searched.

Claims 31 and 33-38 make reference to the products of claims 28 and 30. Thus, the subject-matter of these claims referring to claims 28 and 30 has also not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 03 00211

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-41, 43, 45-47, 49-51, 53, 54 (all entirely); 42, 44, 48, 52 (all partially)

Tyrosine kinase inhibitor proteins, vectors comprising DNA encoding such inhibitors, methods involving said products, methods for activating c-Abl, for producing c-Abl, or for screening for a compound that restores autoinhibition of c-Abl in vivo.

c-Abl protein as defined in claims 42 and 43, wherein a protease cleave site is introduced by genetic engineering, nucleic acid as defined in claim 48, and a transgenic animal comprising a nucleic acid molecule according to claim 48.

2. Claims: 42, 44, 48, 52 (all partially)

c-Abl protein as defined in claim 42, wherein a protease cleave site is not introduced by genetic engineering, nucleic acid as defined in claim 48, and a transgenic animal comprising a nucleic acid molecule according to claim 48.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 03/00211

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0194408	A	13-12-2001	AU	7441601 A	17-12-2001
			EP	1290022 A1	12-03-2003
			WO	0194408 A1	13-12-2001
WO 03031608	A	17-04-2003	WO	03031608 A2	17-04-2003